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Functional connectivity of language networks after perinatal stroke

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ABSTRACT

Successful language acquisition during development is imperative for lifelong function. Complex language networks develop throughout childhood. Perinatal stroke may cause significant language disabilities but function can also be remarkably normal. Studying such very early brain injury populations may inform developmental plasticity models of language networks.

We examined functional connectivity (FC) of language networks in children with arterial and venous perinatal stroke and typically developing controls (TDC) in a population-based, controlled, cohort study. Resting state functional MRI was performed at 3 T (TR/TE = 2000/30 ms, 150 volumes, 3.6mm^3 voxels). Seed-based analyses used bilateral inferior frontal and superior temporal gyri. A subset of stroke participants completed clinical language testing.

Sixty-six children participated (median age: 12.85 ± 3.8y, range 6–19; arterial $N = 17$; venous $N = 15$; TDC $N = 34$]. Children with left hemisphere strokes had comparable FC in their right hemispheres compared to TDC. Inter- and intra-hemispheric connectivity strengths were similar between TDC and PVI but lower for AIS. Reduced FC was associated with poorer language comprehension.

Language networks can be estimated using resting-state fMRI in children with perinatal stroke. Altered connectivity may occur in both hemispheres, is more pronounced with arterial lesions, and is associated with clinical function. Our results have implications for therapeutic language interventions after early stroke.

1. Introduction

Successful language acquisition during development is imperative for lifelong functioning. Despite a substantial literature, identification of the precise neural substrates of language development remain elusive. Historically, clinical brain lesion studies in adults have provided evidence of functional specificity (Broca, 1861; Wernicke, 1874). More recent evidence using functional magnetic resonance imaging (fMRI) confirms that strongly left-lateralized, perisylvian networks involving inferior frontal gyrus (IFG), superior temporal gyrus (STG) and middle temporal gyrus (MTG) often mediate key language processes (Ardila et al., 2016; Friederici, 2011; Poldrack et al., 1999). Dorsal and ventral white matter (WM) structural pathways subserving language networks have also been reliably identified using diffusion imaging tractography (Catani et al., 2005; Saur et al., 2008; Skeide et al., 2016). Arcuate (AF) and superior longitudinal fascicles (SLF) are thought to form the dorsal language pathway and the uncinate fasciculus (UF) and/or extreme capsule, the ventral portion.

Such complex language networks are not present at birth (Perani et al., 2011) but develop throughout childhood (Brauer and Friederici, 2007; Sachs and Gaillard, 2003). Long-range intra-hemispheric language connections between IFG and the posterior regions of the superior temporal areas remain incompletely developed by age six in typically developing children though inter-hemispheric connections at this age appear stronger than in adults (Friederici et al., 2011). This inter- to intra-hemispheric evolution of language networks may be part of larger “local to global” connectivity changes that occur during the normal course of development (Fair et al., 2009). There is also mixed evidence to suggest that left lateralization of language in IFG occurs relatively late in development (i.e., at least 10 years of age) and that

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younger children show more bilateral activations compared to older (Brauer and Friederici, 2007; Holland et al., 2001; Schlaggar et al., 2002; Szaflarski et al., 2006; Ulualp et al., 1998).

Damage to the brain before or during the critical period of language development has the potential to cause lifelong disabilities. Studying patient groups that have incurred early, focal brain injuries provides optimal opportunity to explore compensatory developmental plasticity in language networks. Perinatal stroke accounts for most hemiparetic cerebral palsy (Dunbar and Kirton, 2018). Cognitive and behavioural disorders as well as epilepsy are also common (Kirton, 2013a). Recent advances in imaging have facilitated more accurate diagnosis, classification, and outcome prediction in perinatal stroke. Neonatal arterial ischemic stroke (NAIS) most commonly involves a middle cerebral artery infarction and patients may present with focal seizures in the first few days of life (Kirton et al., 2011). Arterial presumed perinatal ischemic stroke (APPIS) is similar but with later diagnosis when an infant shows early motor asymmetry. Conversely, periventricular venous infarction (PVI) is due to in utero germinal matrix hemorrhage with secondary medullary venous infarction with more isolated subcortical white matter damage (Kirton et al., 2008). As a focal, unilateral injury of defined timing at the beginning of life, perinatal stroke is an ideal human model in which to study developmental plasticity (Kirton, 2013a, 2013b).

Remarkably, many children with large perinatal strokes have relatively intact functional language. Deficits may only become apparent when testing specific higher-level functions (Ballantyne et al., 2007; Ballantyne et al., 2008; Lee et al., 2005; Northam et al., 2018; Reilly et al., 1998; Westmacott et al., 2010). Further, the side of the lesion has remarkably little effect on language outcomes aside from subtle differences on comprehensive testing (Ballantyne et al., 2007; Staudt et al., 2002). This is presumably because lateralization of language has not yet started at the time of injury whereby developmental plasticity can then result in effective bilateral or right hemispheric language organization (Ballantyne et al., 2007; Lidzba et al., 2017; Schlaug, 2018; Westmacott et al., 2010). Accordingly, age is also related to post-stroke lateralization and subsequent function for children incurring stroke after the perinatal period (Carlson et al., 2016; Ilves et al., 2014; Szaflarski et al., 2014). While task functional MRI has helped characterize such developmental language organization, understanding of the integrated language network is limited.

Resting state (RS) fMRI may help elucidate the development of the language network in a task-free manner which lends itself to pediatric populations. RS-fMRI measures low-frequency fluctuations in the blood-oxygen level dependent (BOLD) response at rest, indirectly inferring functional connectivity between regions of interest (Biswal et al., 1995). Using RS-fMRI, intrinsic language connectivity patterns of children longitudinally from age 5 to age 6 have been described (Xiao et al., 2015). Further, resting state analyses of language network functional connectivity have demonstrated considerable temporal reliability and identification of lateralization (Xiang et al., 2010; Zhu et al., 2014). Early studies suggest RS-fMRI approaches are feasible in children with perinatal stroke (Ilves et al., 2014) suggesting a utility toward understanding the neuroplastic mechanisms operating during language development.

The objective of this study was to examine the topography and strength of functional connectivity (FC) within language networks in children with perinatal stroke. We hypothesized that in left hemisphere stroke participants, language networks would have different topography and strength compared to TDC while networks in right hemisphere stroke patients would more closely resemble those of TDC. We also hypothesized that language FC would positively correlate with clinical language function.

2. Methods

2.1. Participants

Stroke participants were recruited via the Alberta Perinatal Stroke Project (APSP), a population-based research cohort (Cole et al., 2017). Inclusion criteria were: (1) unilateral, MRI-confirmed perinatal stroke according to previously validated criteria (Kirton et al., 2008) NAIS, APPIS, or PVI; (2) current age 6 to 19 years and term birth (> 36 weeks), and (3) symptomatic hemiparetic cerebral palsy (HCP) [Pediatric Stroke Outcome Measure (PSOM) score > 0.5 (Kitchen et al., 2003) and Manual Ability Classification System (MACS) score I-IV (Arner et al., 2005) and perceived functional limitations by child and parent]. Children with additional neurodevelopmental or psychiatric conditions, clinical or imaging evidence of bilateral or more diffuse injury, or unstable epilepsy were excluded. Children with NAIS and APPIS were combined into a single group (AIS) due to similar mechanism of injury.

Typically developing control (TDC) volunteers were recruited through an established healthy controls program. TDC participants were right handed by self-report, aged 6 to 19 years, and had no MRI contraindications, neurodevelopmental, or psychiatric conditions. TDC participants were sex and age (± 1 year) balanced with stroke cases. For all participants, informed parental consent and participant assent were attained in accordance with the University of Calgary Research Ethics Board.

2.2. Imaging

Images were acquired at the Alberta Children's Hospital Diagnostic Imaging Suite using a 3.0 Tesla GE MR750w MRI scanner (GE Healthcare, Waukesha, WI) with an MR Instruments 32-channel head coil. High-resolution anatomical T1-weighted fast spoiled gradient echo (FSPGR BRAVO) images were acquired in the axial plane [166 slices, no skip; voxel size = 1.0 mm isotropic; repetition time (TR) = 8.5 ms; echo time (TE) = 3.2 ms; matrix = 256 × 256].

2.3. Lesion characterization

For AIS patients, binary masks of stroke lesions were created using native space T1-weighted images via a semi-automated demarcation process within MRIcron (Rorden et al., 2007). This three-dimensional process fills a specified lesioned area (based on image intensity) until lesion boundaries are encountered. Images were reviewed slice-by-slice and manually edited to ensure lesion selection accuracy after which lesion volume (in cubic centimetres (cc)) was extracted. Lesion masks were subsequently warped into standard Montreal Neurological Institute (MNI) space using a 152-average template within the Normalise function in SPM (Statistical Parametric Mapping (SPM version 12b [5763], Wellcome Trust Centre for Neuroimaging, UCL, London, UK). Lesion overlay maps (Fig. 1) were then generated for patients with left and right hemisphere AIS to illustrate lesion overlap within the two groups. Relative lesion volume (in percent) was calculated as such: (Lesion volume/GM + WM volume)*100.

Since PVI lesions typically involved a dilation of one of the lateral ventricles, ventricle asymmetry was approximated by demarcating both ventricles including the periventricular lesion (using the technique described above) then subtracting the volume (in cc) of the non-lesioned ventricle from the lesioned (Table 1).

2.4. Resting state fMRI

Resting state fMRI acquisition used 150 T2*-weighted whole brain echo planar volumes (EPI; 36 interleaved contiguous slices; voxel size = 3.6 mm isotropic; TR/TE = 2000/30 ms; matrix = 64 × 64; duration = 5:00). Five volumes (10s) were discarded at the beginning

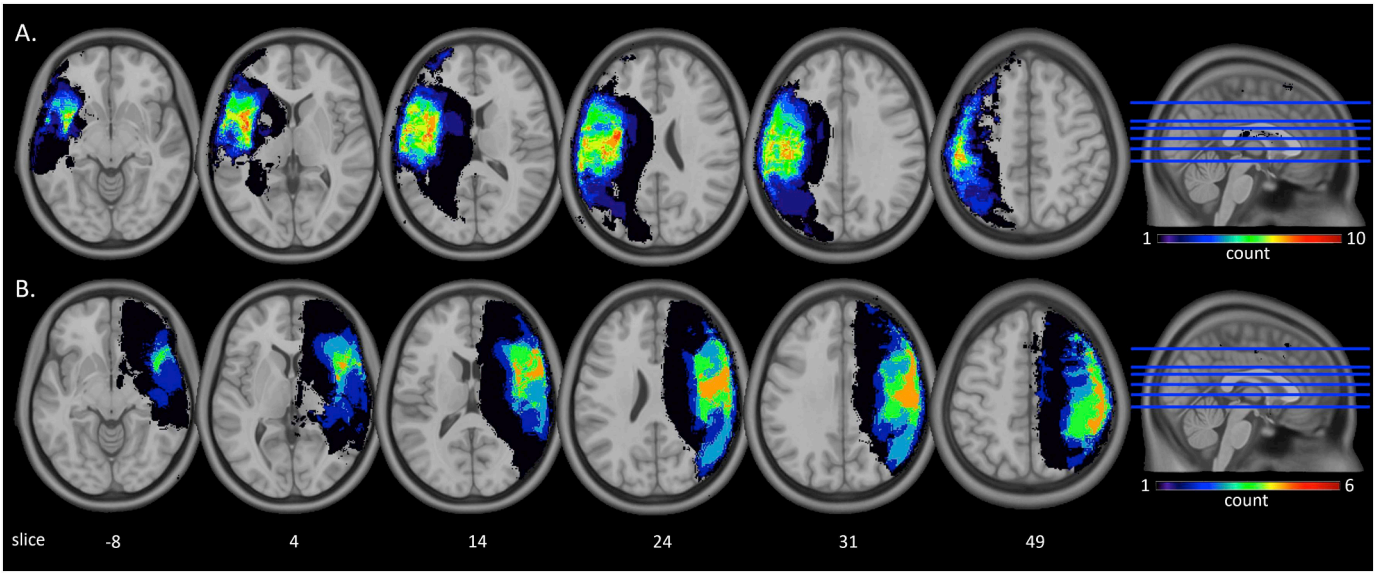

Fig. 1. Lesion overlay maps for participants with left (A) and right (B) hemisphere arterial (AIS) strokes. Shown are heat maps corresponding to the number of patients that have a lesion in that area overlaid on axial slices from a standard template in MNI space (MNI152). Red shading indicates most lesion overlap and blue/black least overlap. Images are presented in neurological convention (i.e., right hemisphere is on the right side). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of each functional run to attain magnetic field equilibrium. During the sequence, participants were asked to fixate on a centrally presented cross while thinking of nothing in particular.

Resting state functional analyses were performed using the Functional Connectivity Toolbox (CONN; Whitfield-Gabrieli and Nieto-Castanon, 2012), part of SPM12 running within Matlab (Mac i64 version R2016b, Mathworks, Natick, MA). Preprocessing utilized the standard CONN pipeline including slice timing correction, realignment, co-registration, and calculation of head motion parameters. Co-registered images were segmented using standard SPM tissue probability maps and were reviewed slice-by-slice to ensure that lesioned areas were correctly categorized as cerebral spinal fluid. Images were normalised into MNI space using the standard 152-average template and smoothed with a 6 mm^3 full-width at half-maximum (FWHM) Gaussian kernel. Head motion and other outliers were identified using the Artifact Repair Toolbox (Mazaika et al., 2007) with global mean signal greater than z = 5, exceeding 0.9 mm of translational movement or exceeding 0.025 rad of rotational movement. Identified volumes were subsequently de-weighted in the general linear regression model (GLM) as were CSF and WM time courses.

Subsequent seed-to-voxel and seed-to-seed analyses for the whole brain were performed using six seeds of interest. Four seeds were predefined based on an independent component analysis of the Human Connectome Project data performed in CONN and provided by the developers for reference (Whitfield-Gabrieli and Nieto-Castanon, 2012). These included the left (LIFG: MNI -51, 26, 2) and right inferior frontal gyri (RIFG: MNI 54, 28, 1), left (LSTG: MNI -57, −47, 15) and right posterior superior temporal gyri (RSTG: MNI 59, −42, 13). Seeds in the left (LFP) and right (RFP) frontal poles were used as non-language network reference points (negative controls) for comparison to establish functional specificity and were selected from a validated atlas (FSL Harvard-Oxford atlas) provided in CONN. Seed-to-voxel analyses were carried out using left and right IFG seeds and statistical significance threshold was set to $p < .05$ (cluster-size false discovery rate (p_{FDR}) corrected). For seed-to-seed analyses, Pearson bivariate correlations were performed between each of the ROIs to examine connectivity and Fisher-transformed Pearson r values are reported. FC between language seeds (LIFG, RIFG, LSTG and RSTG) were subsequently used to quantify group level connectivity.

Second-level seed-to-voxel contrasts were performed to investigate statistical differences in connectivity between TDC, left and right stroke. For these contrasts (TDC > left stroke and TDC > right stroke), significance threshold was set to $p_{FDR} < 0.05$ (cluster-size corrected).

A laterality index (LI) was also calculated to quantify the degree of laterality in FC strength. Values greater than zero represent right hemisphere lateralization, less than zero left lateralization, and values close to zero indicate more symmetrical, bilateral organization. LI was calculated as follows where FC in the right hemisphere is represented as $FC_{RIFG\text{-}RSTG}$ and the left as $FC_{LIFG\text{-}LSTG}$.

$$LI = \frac{FC_{RIFG-RSTG} - FC_{LIFG-LSTG}}{FC_{RIFG-RSTG} + FC_{LIFG-LSTG}}$$

2.5. Neuropsychological outcomes

A subset of stroke participants were referred for neuropsychological (NP) testing if clinically indicated and deemed a benefit by the referring pediatric neurologist. Common reasons for not being referred for NP testing included 1. No concerns regarding cognitive functioning or 2. Profound developmental delays preventing engagement in testing. Percentile scores are reported for all NP tests, quantifying cognitive function relative to age-adjusted norms (Table 1). For all NP tests, higher percentile scores indicate better performance. The mean percentile score for the normative sample is standardized to be 50% and patient scores falling between the 25th–75th percentiles are considered in the average range.

Measures of expressive language [WISC-IV Vocabulary & Comprehension, Developmental Neuropsychological Assessment 2nd Ed. (NEPSY-II) Word Generation (Sematic and Initial Letter)] and receptive language [Woodcock-Johnson 3rd Ed. (WJ-III) Understanding Directions] were included to quantify language function. Standardized measures of intellectual functioning [Wechsler Intelligence Scale for Children 4th Ed. (WISC-IV) Full Scale IQ] and processing speed (WISC-IV Processing Speed Index) were included to characterize level of functioning in our sample.

Tests of verbal memory [California Verbal Learning Test – Children (CVLT-C) Total trials 1–5, Children's Memory Scale (CMS) Stories (Delayed)], and visual memory [Continuous Visual Memory Test

Table 1
Participant demographics by group and stroke hemisphere.

Demographics by participant group	AIS (*N* = 17)	PVI (*N* = 15)	TDC (*N* = 34)
Mean|Median age (SD) [range] years	14.0|14.2 (4.1) [6.6–19.0]	12.8|11.4 (4.0) [6.7–19.7]	13.2|13.1 (3.6) [6.5–19.0]
Sex [%]			
Male	*N* = 10 [58.8%]	N = 10 [66.7%]	*N* = 19 [55.8]
Female	*N* = 7 [41.2%]	*N* = 5 [33.3%]	N = 15 [41.7%]
Side of stroke (MRI) [%]			
Left	N = 12 [70.6%]	N = 9 [60.0%]	–
Right	N = 5 [29.4%]	*N* = 6 [40.0%]	–
Stroke volume mean (SD) [range]			
GM/WM Lesion volume (cc)	64.6 (75.0) [2.9–311.5]	–	–
GM/WM Relative lesion volume (%)	5.9 (8.7) [0.22–36.8]	–	–
Ventricle asymmetry (cc)	-	6.2 (11.9) [−2.6–38.9]	–

Demographics by Stroke Side	Left (*N* = 21)	Right (N = 11)
Mean|Median age (SD) [range] years	13.1|12.4 (4.2) [6.6–19.0]	14.1|13.1 (3.8) [9.1–19.7]
Sex [%]		
Male	N = 12 [57.1%]	N = 8 [72.7%]
Female	N = 9 [42.9%]	N = 3 [27.2%]
Mechanism of stroke [%]		
AIS	*N* = 12 [57.1%]	N = 5 [45.5%]
PVI	*N* = 9 [42.9%]	N = 6 [54.5%]

Cognitive functioning (mean %ile (SD) [range])	AIS & PVI	N
Intellectual functioning		
WISC-IV – Full scale IQ	21.3 (24.9) [0.4–79]	11
WISC-IV – Processing speed index	13.1 (14.2) [0.1–50]	16
Expressive language		
WISC-IV – Vocabulary	22.5 (20.1) [0.4–75]	16
WISC-IV – Comprehension	16.3 (11.7) [2–37]	7
NEPSY-II – Word Generation (Semantic)	50.1 (28.6) [0.1–99]	16
NEPSY-II – Word Generation (Initial Letter)	8.5 (9.3) [0.4–25]	15
Receptive language		
WJ-III – Understanding Directions	48.0 (31.2) [7–95]	11
Verbal memory		
CVLT-C – Total trials 1–5	58.8 (27.2) [8–95]	156
CMS – Stories (Delayed)	60.6 (27.4) [5–95]	8
Visual memory		
CVMT – Total	40.6 (32.8) [10–90]	7
CMS – Faces (Delayed)	29.6 (30.5) [0.4–75]	8

Note: Cognitive variables are expressed in group mean percentiles (SD) [range] where 25–75% are considered in the average range compared to typically developing peers. AIS – Arterial Ischemic Stroke, PVI – Periventricular venous infarction, TDC – Typically developing controls, SD – standard deviation, MRI – Magnetic resonance imaging confirmed side of stroke, cc – cubic centimetres, Ventricle asymmetry – volume of the non-lesioned ventricle subtracted from the lesioned. WISC-IV – Wechsler Intelligence Scale for Children (4th ed.), NEPSY-II – Developmental Neuropsychological Assessment (2nd ed.), WJ-III – Woodcock–Johnson Tests of Cognitive Abilities (3rd ed.), CVLT-C – California Verbal Learning Test (Children's version), CMS – Children's Memory Scale, CVMT – Continuous Visual Memory Test.

(CVMT) Total score, CMS Faces (Delayed)] were also collected. Verbal memory measures were included as they concurrently measure both language and memory function. Visual memory tasks were included to quantify memory function with minimal language component. A comparison between performance on verbal and visual memory tasks was intended to investigate a possible dissociation between the two, reflecting that deficits on verbal memory tasks may not be memory dysfunction per se but rather language dysfunction reflected using a memory test.

2.6. Statistical analyses

The Statistical Package for the Social Sciences (IBM SPSS Version 19 for Windows, Chicago, USA) was used to complete statistical analyses. Distribution normality was determined using a Shapiro-Wilk test. Pearson correlations were performed between age and connectivity strengths. Subsequently, a mixed design analysis of variance (ANOVA) was performed to explore differences in FC strength among participant groups (AIS, PVI, TDC) and regions of interest (ROI). In a separate analysis, participant groups were re-divided according to stroke side (combining AIS and PVI) to investigate differences in network topology between those with left and right stroke. Subsequent post-hoc Kruskal-Wallis, Mann-Whitney U, and Student *t*-tests (paired or independent, as appropriate) were conducted to examine pair-wise contrasts of interest. Equality of variance was tested with Levene's test. One-sample Wilcoxon Signed Rank tests examined whether LI was different from zero. Effect sizes for the Wilcoxon tests were calculated as below where r represents the effect size, Z is the standardized Wilcoxon test statistic and N is the total number of observations (Rosenthal, 1991):

$$r = \frac{Z}{\sqrt{N}}$$

Pearson's correlation coefficients (or Spearman's rho as appropriate) were performed between FC and language function. Statistical significance threshold was set to $p < .05$ (corrected for multiple comparisons where FDR < 0.05 (Benjamini and Hochberg, 1995)).

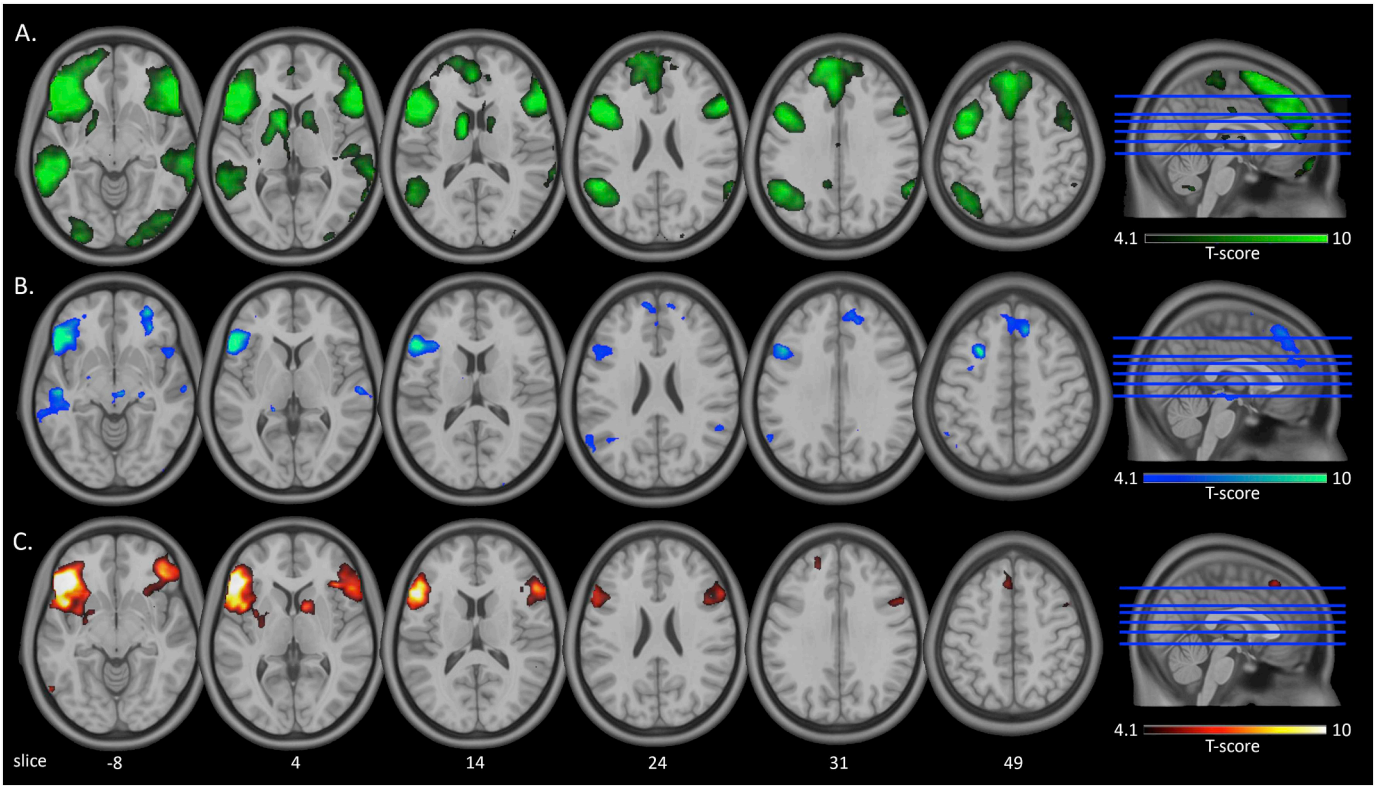

Fig. 2. Seed-to-voxel heat maps illustrating significant FC when seeding left inferior frontal gyrus (IFG) in TDC participants (A), patients with right (B), and left (C) hemisphere (both AIS and PVI) stroke. Shown are FC T-score maps overlaid on a MNI152 template image in standard space. T-score threshold ($T > 4.1$) for all panels was set to reflect the smallest sample size (right stroke, $N = 11$) for image comparability. Images are displayed in neurological convention (right side of image is right side of brain) and slice numbers represent MNI coordinates.

3. Results

3.1. Participants

Sixty-eight participants (age range 6–19 years; 27 females) were recruited [AIS, $N = 17$; PVI, $N = 15$; TDC, $N = 36$]. Table 1 details additional demographic information as well as sample sizes for the subset that completed cognitive testing. Two male control participants were subsequently excluded due to excessive head motion resulting in a final TDC sample of 34. Lesion overlay maps are illustrated in Fig. 1 to visually characterize lesions in the AIS patient group by hemisphere. Lesion size (raw or relative) was not significantly different between left and right AIS stroke patient groups. For PVI participants, five had subcortical grey matter involvement. Average age and gender proportions were not significantly different between groups. Mean head motion did not differ between the three participant groups and was not significantly correlated with strength of any seed-to-seed connectivities.

3.2. Seed-to-voxel connectivity

Seed-to-voxel analyses using left IFG suggested significant FC with other language areas for all participant groups albeit with different strengths. Fig. 2 illustrates seed-to-voxel results using the T-score threshold ($T > 4.1$) from the group with the smallest sample size (right stroke, $N = 11$) for image comparability in all panels. When seeding left IFG in TDC participants, areas related to language such as left STG, right IFG and superior frontal gyri (SFG) were found to be highly functionally connected.

For stroke patients, a similar pattern was found (Table 2). When seeding left IFG in patients with a right hemisphere stroke (Fig. 2B), significant clusters were found in language areas of the left temporal lobe (middle and inferior temporal gyri) and frontal lobe (SFG). Areas in the right hemisphere were also significantly functionally connected (middle temporal gyrus, superior frontal gyrus). When seeding left IFG in those with left stroke, connectivity was seen with homologous right IFG but not temporal areas (Fig. 2C).

To examine symmetry of IFG connectivity, right IFG was also seeded for all participant groups (Fig. 3). TDC participants showed a very similar pattern with both right and left IFG seeds (Fig. 2A vs. Fig. 3A). Participants with right stroke showed very little connectivity with other language areas (Fig. 3B). When seeding right IFG in patients with left stroke, areas of significant FC were found to be SFG, left superior temporal gyrus as well as cingulate gyrus. Areas associated with language function in the left hemisphere such as middle and inferior temporal gyri also appeared to be connected.

When seeds were placed in left and right superior temporal gyri (STG; Figs. S1 and S2), similar patterns were seen for TDC participants showing largely bilateral, symmetrical connectivity patterns. Right stroke participants showed more unilateral connectivity patterns when seeding with left STG (Fig. S1 panel B) compared to TDC. Left stroke participants showed more bilateral connectivity between temporal regions than right stroke but less than TDC (Fig. S1 panel C).

3.3. Second-level TDC > stroke contrasts

Significantly higher connectivity was found for TDC compared to participants with left stroke (Fig. 4) when seeding left IFG. Differences were found in left IFG, left middle temporal gyrus, left caudate nucleus and left anterior thalamus. A similar pattern was found in the left anterior thalamus in children with right stroke when seeding the right IFG, however differences were much smaller (likely due to the smaller sample).

Table 2
Seed-to-voxel group mean connectivity for patients with right and left stroke.

Participants with right hemisphere stroke (N = 11)					
Seed: Left Inferior Frontal Gyrus (IFG)	Cluster (X Y Z)			Size (voxels)	p FDR
Left Inferior Frontal Gyrus (IFG)	−54	24	−2	2980	p < .0001
Left & Right Superior Frontal Gyrus (SFG)	10	30	48	860	p < .0001
Left Middle Temporal Gyrus (MTG)	−48	−20	−10	401	p < .0001
Right Frontal Pole (FP)	30	52	−6	205	p < .0001
Left Inferior Temporal Gyrus (ITG)	−50	−2	−34	96	p = .024
Left Angular Gyrus (AG)	−62	−60	30	90	p = .026
Right Middle Temporal Gyrus (MTG)	60	−18	4	80	p = .035
Left Frontal Pole (FP)	−10	58	26	70	p = .049
Participants with left hemisphere stroke (N = 21)					
Seed: Right Inferior Frontal Gyrus (IFG)	Cluster (X Y Z)			Size (voxels)	p FDR
Right Inferior Frontal Gyrus (IFG)	54	26	6	12,842	p < .0001
Left Inferior Frontal Gyrus (IFG)	−52	10	−6	4399	p < .0001
Medial Superior Frontal Gyrus (SFG)	4	26	64	4036	p < .0001
Left Middle Temporal Gyrus (MTG)	−60	−48	24	1497	p < .0001
Left Precentral Gyrus (M1)	−46	−4	46	496	p < .0001
Cingulate Gyrus	−2	−30	46	377	p < .0001
Medial Occipital Lobe	4	−96	0	129	p = .023
Thalamus	4	−8	−4	109	p = .037

Note: p FDR – Cluster-size False Discovery Rate corrected.

3.4. Seed-to-seed language networks

Seed to seed connectivity estimates were measureable for all predefined connections. For the seed-to-seed FC analysis, results of the ANOVA showed a significant main effect for patient group [$F(2,63) = 27.0$, $p < .001$], ROI [$F(3,63) = 33.1$, $p < .001$] as well as a significant patient group by ROI interaction [$F(6,63) = 14.1$, $p < .001$]. Subsequent post-hoc tests were performed to elucidate differences of interest.

Fig. 5A illustrates FC values among language ROIs expressed as group mean Fisher-transformed Pearson bivariate correlation coefficients. TDC participants (panel A) showed a largely bilateral resting

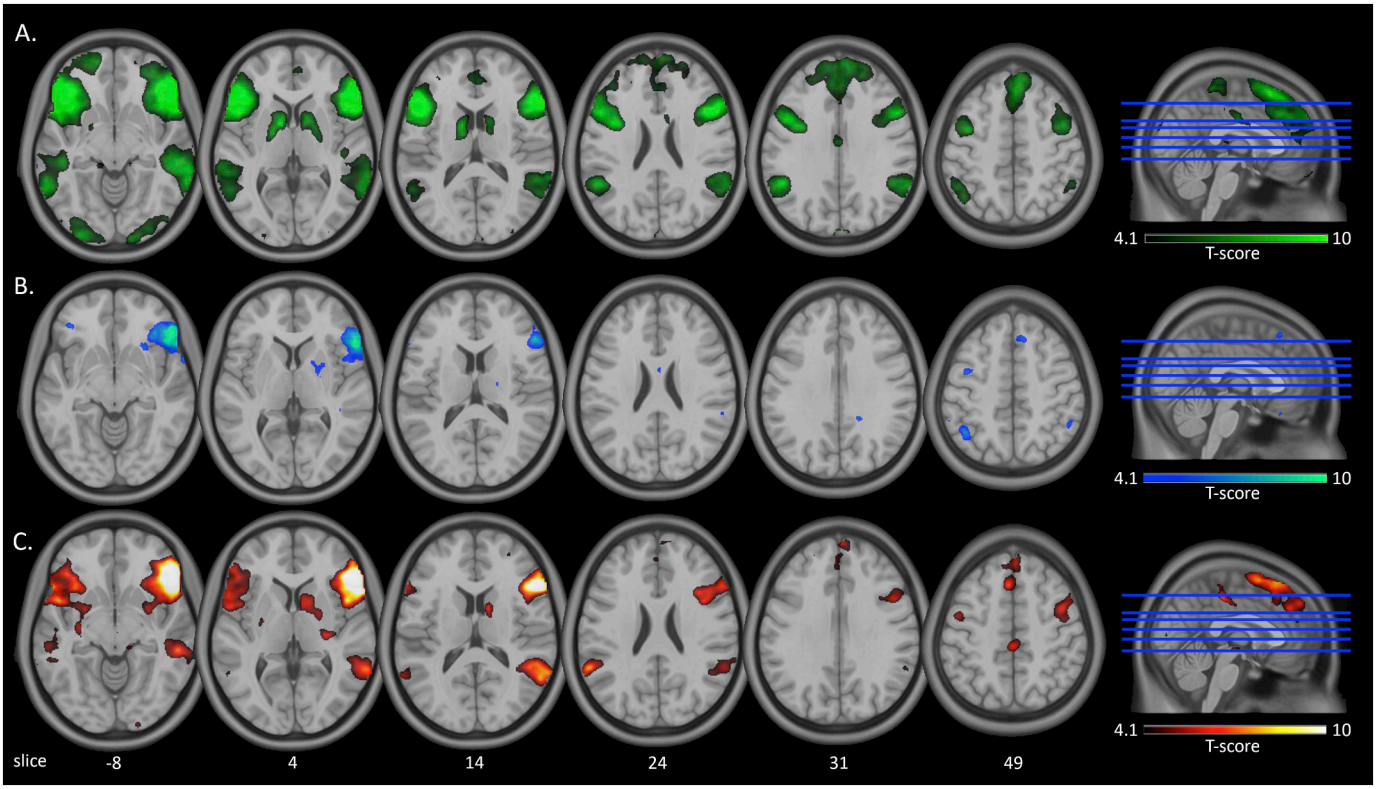

Fig. 3. Seed-to-voxel heat maps illustrating significant FC when seeding right inferior frontal gyrus (IFG) in TDC participants (A), patients with right (B), and left (C) hemisphere (both AIS and PVI) stroke. Shown are FC T-score maps overlaid on a MNI152 template image in standard space. T-score threshold ($T > 4.1$) for all panels was set to reflect the smallest sample size (right stroke, $N = 11$) for image comparability. Images are displayed in neurological convention (right side of image is right side of brain) and slice numbers represent MNI coordinates.

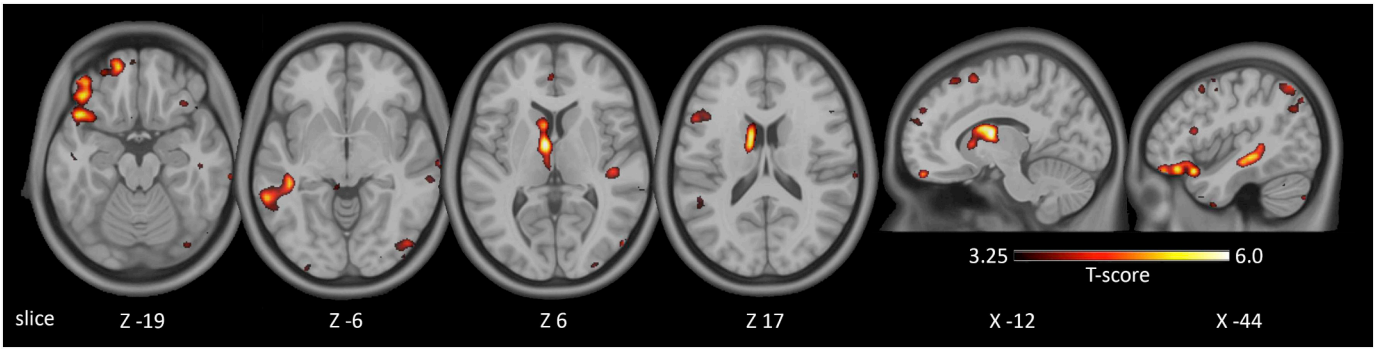

Fig. 4. Statistical contrast between TDC and left stroke participants (TDC > left stroke) when seeding in left IFG. Shown is a T-score heat map overlaid on a MNI 152 template brain in neurological convention (right is on right side). Z and X indicate MNI slices.

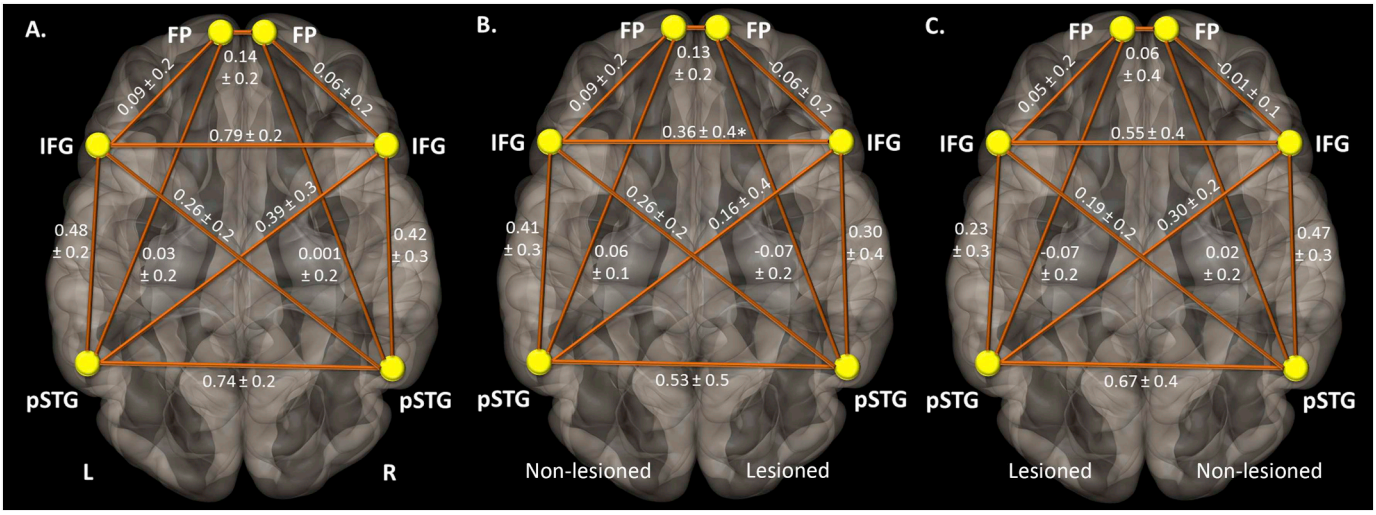

Fig. 5. Group mean functional connectivity (FC) values displaying Fisher-transformed bivariate Pearson correlation coefficients for TDC (A) and patients with right (B) and left (C) hemisphere stroke. Patients with AIS and PVI have been combined on the same figure according to the side of their lesion. IFG – inferior frontal gyrus, pSTG – posterior superior temporal gyrus, FP – frontal pole. Shown are means ± standard deviation. Images are presented in neurological convention (right side of image is right side of brain). *$p < .05$ compared to controls.

language network evidenced by very similar connectivity between IFG and STG on the left side (M = 0.48 ± 0.2) compared to right (M = 0.42 ± 0.3, $p = .27$). Very low connectivity was seen between language seeds and the non-language frontal pole comparison areas (M = 0.05 ± 0.05).

TDC showed significantly higher inter-hemispheric connectivity between left and right IFG (M = 0.79 ± 0.2) compared to intra-hemispheric connectivity (IFG-STG) in both the left (M = 0.48 ± 0.2, t(33) = 6.6, $p < .001$) and right (M = 0.42 ± 0.3, t(33) = 7.3, $p < .001$) hemispheres. This pattern was also observed for inter-hemispheric connectivity between left and right STG (M = 0.74 ± 0.2) compared to intra-hemispheric connectivity (IFG-STG: Left t(33) = 5.0, $p < .001$; Right t(33) = 7.0, $p < .001$). Age was not associated with intra- or inter-hemispheric connectivity.

3.5. Intra-hemispheric connectivity

Intra-hemispheric connectivity in the lesioned hemisphere was significantly lower compared to the non-lesioned hemisphere for left hemisphere stroke (M = 0.23 vs 0.47, $p = .014$) but not for right hemisphere stroke (M = 0.41 vs 0.30, $p = .46$). Age was not significantly related to connectivity within the non-lesioned hemisphere for left or right stroke groups.

Participants with a lesion in the right hemisphere (Fig. 5B) showed similar connectivity between IFG and STG in the left hemisphere (M = 0.41 ± 0.3) compared to TDC (M = 0.48 ± 0.2, $p = .42$) with similar variance in connectivity values. Consistent with TDC, connectivity with the frontal pole reference area was very low (M = 0.08 ± 0.2).

Participants with a lesion in the left hemisphere (Fig. 5C) showed comparable connectivity between IFG and STG in the right hemisphere (M = 0.47 ± 0.3) compared to both the right (M = 0.42 ± 0.3, $p = .43$) and left hemispheres of TDC participants (M = 0.48 ± 0.2, $p = .93$). Connectivity of these areas with the frontal pole reference again was very low (M = 0.005 ± 0.15).

3.6. Inter-hemispheric connectivity

Inter-hemispheric connectivity between left and right IFG was significantly lower for right stroke (M = 0.36 ± 0.4, $p = .014$) with a similar trend observed for left stroke (M = 0.55 ± 0.4, $p = .054$) as compared to TDC (M = 0.79 ± 0.2). Inter-hemispheric connectivity between left and right STG was not different between the three participant groups.

3.7. Laterality index

For all groups, laterality indices demonstrated large variability. LI for TDC was approximately symmetrical indicated by being close to 0 (M = −0.11, median = −0.03, range: −1.82 to 1.58). Age was not related to laterality index in the TDC group ($\rho = 0.21$, $p = .23$). For children with left hemisphere stroke, mean laterality index indicated a

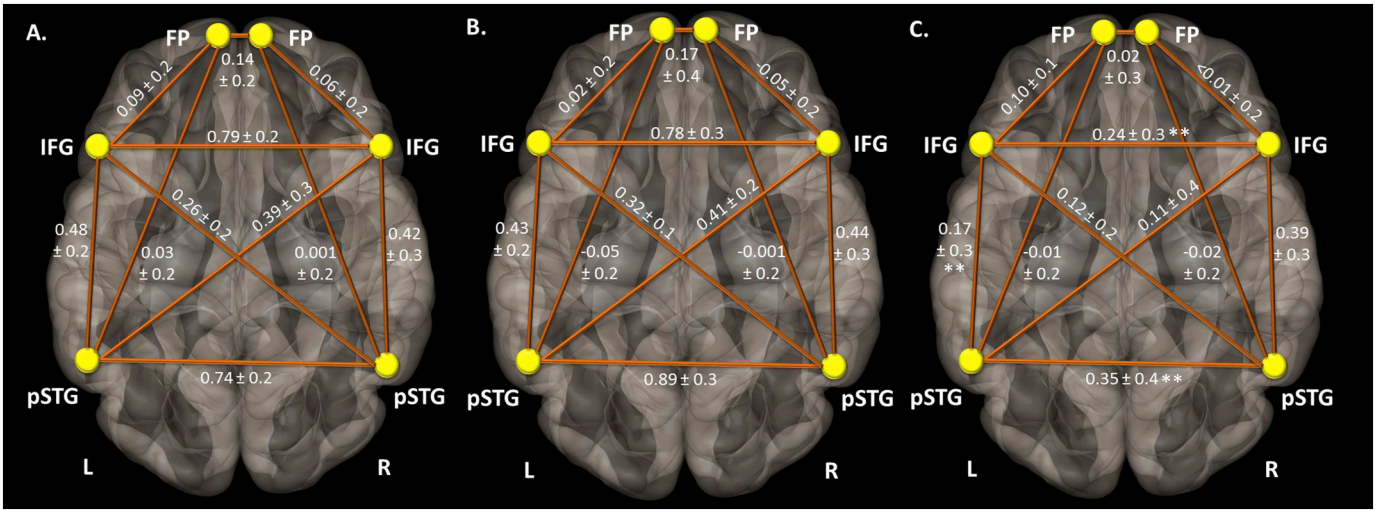

Fig. 6. Group mean functional connectivity (FC) values displaying Fisher-transformed bivariate Pearson correlation coefficients displayed by participant group for TDC (A), PVI (B) and AIS (C). IFG – Inferior frontal gyrus, pSTG – Posterior superior temporal gyrus, FP – Frontal pole. Shown are means ± standard deviation. Images are presented in neurological convention (right side of image is right side of brain). $^{**}p < .01$ compared to controls.

significant right-hemisphere laterality compared to zero (M = +0.71 ± 2.4, Z = 2.0, $p = .046$, effect size $r = 0.44$, median = 0.33, range: −2.73 to 10.5). For children with right hemisphere stroke, laterality appeared left lateralized but statistically was not different from zero (M = -0.85 ± 2.2, Z = -1.16, $p = .25$, effect size $r = 0.35$, median = −0.28, range: −7.04 to 0.99). Age was not associated with laterality index in the right (ρ = 0.02, $p = .96$) or left (ρ = −0.005, $p = .98$) hemisphere stroke groups.

3.8. Connectivity by stroke type

Group differences in FC were seen between stroke types (Figs. 6 & 7). Patients with PVI had similar network connectivity strengths to TDC but were significantly different from AIS. AIS patients showed significantly lower inter-hemispheric FC than both TDC ($p < .01$) and PVI ($p < .01$) between LIFG-RIFG (TDC M = 0.79 ± 0.2; PVI M = 0.78 ± 0.3; AIS M = 0.24 ± 0.3). The same pattern was seen for inter-hemispheric connectivity between LSTG-RSTG (TDC M = 0.74 ± 0.2; PVI M = 0.89 ± 0.3; AIS M = 0.35 ± 0.4; both p's < 0.01).

Differences in intra-hemispheric FC showed a similar pattern for LIFG-LSTG (Figs. 6 & 7B, TDC M = 0.48 ± 0.2; PVI M = 0.43 ± 0.2; AIS M = 0.17 ± 0.3) where AIS FC was significantly lower than both TDC (p < .01) and PVI ($p < .05$). No significant differences were observed between the groups for RIFG-RSTG connectivity. Age was not significantly associated with connectivity within the AIS group but inter-hemispheric FC between LSTG and RSTG was negatively related to age for the PVI group (ρ = −0.53, p = .04).

3.9. Cognitive functioning

Participants with stroke (AIS and PVI) were combined together into

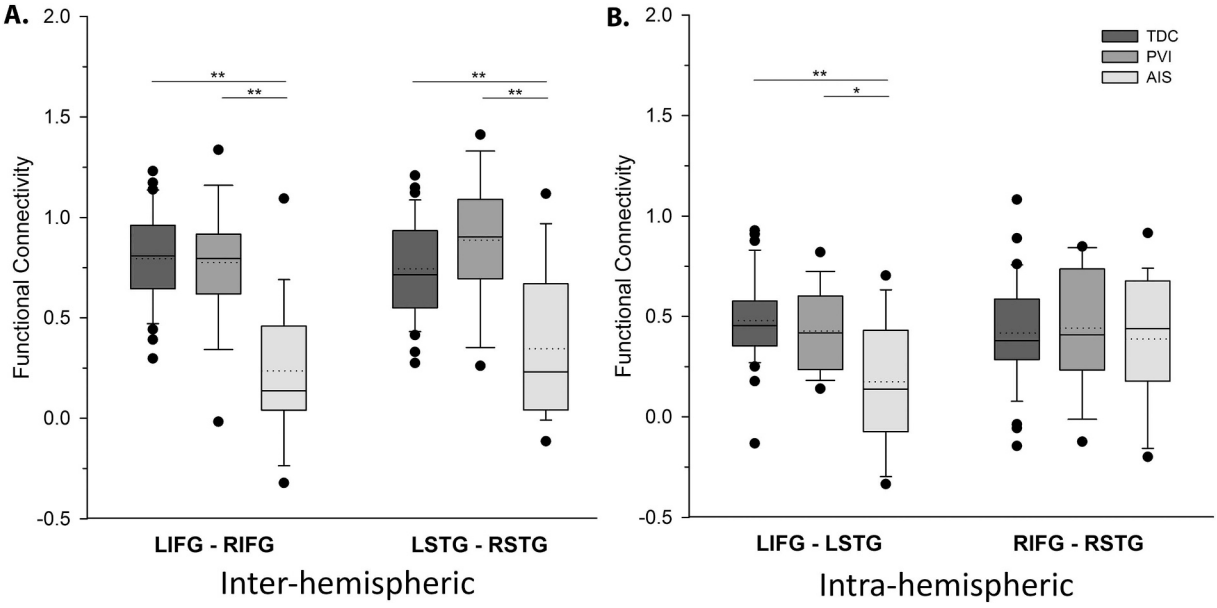

Fig. 7. Boxplots illustrating group means for inter-hemispheric (A) and intra-hemispheric (B) functional connectivity by participant group (collapsing over lesion side). Shown are median (solid line) and mean (dotted line) Fisher-transformed Pearson correlation coefficients as well as quartile ranges and outliers (filled circles). $^{**}p < .01$, $^{*}p < .05$. TDC – typically developing controls, PVI – periventricular venous infarction, AIS – Arterial ischemic stroke, IFG – Inferior frontal gyrus, STG – Posterior superior temporal gyrus, R – right, L – left.

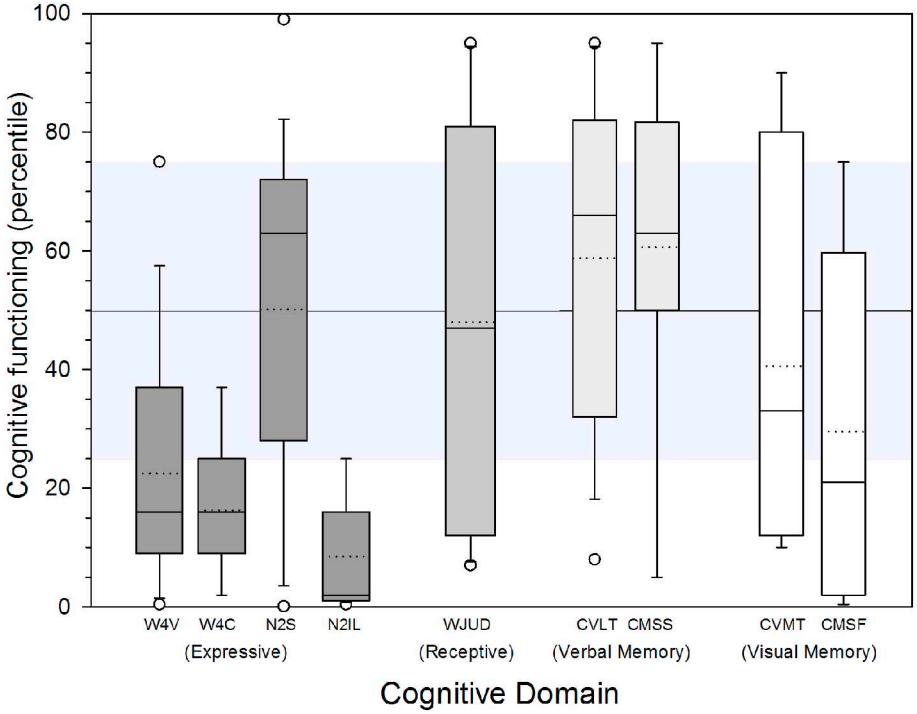

Fig. 8. Cognitive functioning as measured by clinical neuropsychological testing for stroke participants. Values are percentiles in comparison to an age-matched peer group. W4V – WISC-IV Vocabulary, W4C – WISC-IV Comprehension, N2S – NEPSY-II Word Generation (Sematic), N2IL – NEPSY-II Word Generation (Initial Letter), WJUD – Woodcock-Johnson III Understanding Directions, CVLT – California Verbal Learning Test – Children's Edition, CMSS – Children's Memory Scale Stories, CVMT – Continuous Visual Memory Test, CMSF – Children's Memory Scale Faces. The shaded area represents the 25–75 percentile range and the horizontal rule demarcates the 50th percentile (i.e., average functioning in a TDC group). Table 1 contains sample sizes for each cognitive test.

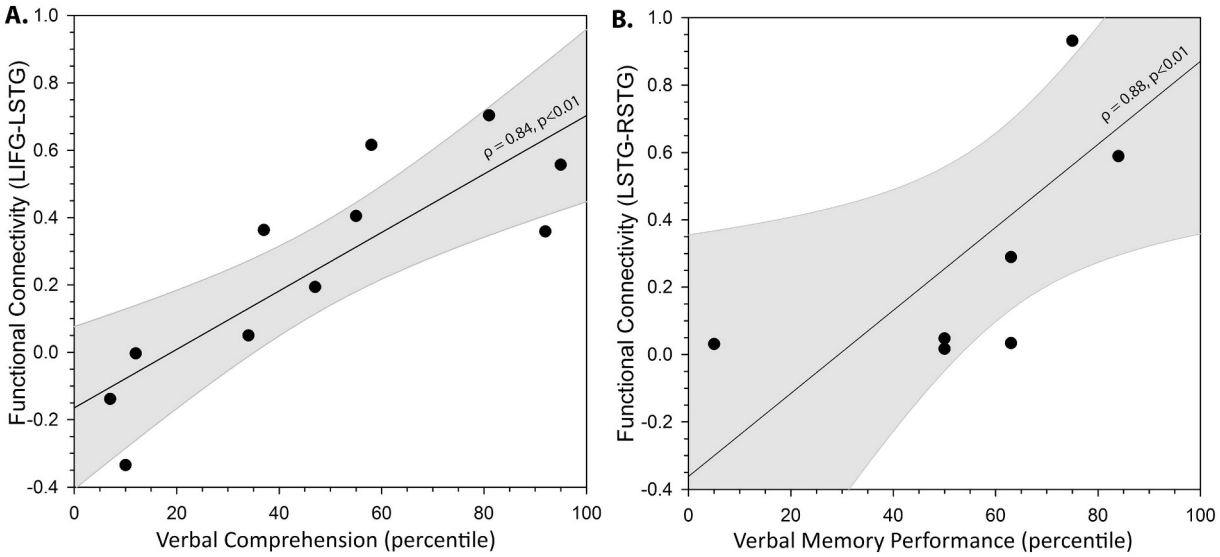

Fig. 9. Scatterplots illustrating correlations between intra-hemispheric functional connectivity (LIFG-LSTG) and verbal comprehension (WJ-III Understanding Directions, $N = 11$) (A) and inter-hemispheric FC (LSTG-RSTG) and verbal memory performance (CMS Stories, $N = 8$) (B) for a subset of participants with clinical neuropsychological testing. This cohort includes all patients who performed language testing, regardless of side of lesion. WJ-III – Woodcock–Johnson Tests of Cognitive Abilities (3rd ed.), CMS – Children's Memory Scale, IFG – Inferior frontal gyrus, pSTG – Posterior superior temporal gyrus, R – right, L – left, ρ – Spearman's rho. Shaded areas represent 95% confidence intervals.

one group to maximize statistical power when investigating cognitive functioning. Functioning varied across NP domains for participants with stroke compared to TDC (Table 1, Fig. 8). Measures of expressive and receptive language ranged from low average to high average, with the exception of an initial letter word generation task (NEPSY-II Word Generation (Initial Letter); $N = 15$, M = 8.5 percentile ± 9.3) and an expressive task (WISC-IV Comprehension; $N = 7$, M = 16.3 percentile ± 11.7) that showed low performance on the group level.

Several measures of cognitive functioning significantly correlated with the strength of both inter- and intra-hemispheric FC between language nodes. Specifically, a strong positive correlation was found between verbal comprehension (i.e., performance on the WJ-III Understanding Directions task) and intra-hemispheric FC between LIFG-LSTG ($N = 11$, $\rho = 0.84$, $p < .01$, Fig. 9A).

No significant correlations were found for FC and measures of expressive language (WISC-IV Vocabulary & Comprehension), or word generation tasks (NEPSY-II Word Generation Initial Letter or Semantic Category) although there was a modest potential association between LIFG-LSTG FC and performance on the NEPSY-II Initial Letter word generation task (N = 15, $\rho = 0.50$, $p = .06$).

An interesting dissociation was found for memory performance (Fig. 9B) indicating that inter-hemispheric FC between LSTG-RSTG was strongly correlated with performance on a verbal memory test with a comprehension component (CMS Stories: $N = 8$, $\rho = 0.88$, $p < .01$)

but not performance on visual memory tests (CMS Faces: N = 8, $\rho = 0.07$, $p = .87$; CVMT: $\rho = -0.29$, $p = .54$). Performance on a word list learning test was also not significantly related to LSTG-RSTG connectivity strength (CVLT-C: N = 15; $\rho = -0.12$, $p = .67$).

AIS lesion size (raw and relative) was not significantly associated with measures of cognitive functioning.

4. Discussion

We provide evidence that functional connectivity of language networks is altered after perinatal stroke. Children with left hemisphere perinatal stroke appeared to have comparable functional connectivity strengths between language areas in their right hemispheres as compared to TDC. Both inter- and intra-hemispheric connectivity strengths were similar between TDC and children with PVI but were lower for children with AIS. Decreased FC appears to be associated with elements of poorer language performance on tasks with a substantial comprehension component.

Findings within our typically developing control sample supported the ability of our methods to image functional connectivity within language networks. Intra-hemispheric estimates were similar between the left and right hemispheres (albeit with substantial variability). This symmetrical bi-hemispheric pattern in our sample was somewhat surprising since past literature suggests that left lateralization may be established by around 10 years of age (Holland et al., 2001). Similarly, we also expected to find a positive association between laterality index and age given that left hemisphere lateralization is thought to increase during childhood and adolescence. It could be that by chance our TDC sample was composed primarily of children with bilateral language representations despite all being right-handed by self-report. Another more likely possibility is that development of left lateralization of functional connectivity takes place later in life consistent with task fMRI studies reporting lateralization plateaus occurring between 20 and 25 years (Szaflarski et al., 2006; Szaflarski et al., 2012). Literature investigating language using combined fMRI and diffusion imaging methods also report that during childhood networks are not fully adult-like and may continue to develop into early adulthood (Brauer et al., 2011).

We also found higher inter-hemispheric functional connectivity strengths than intra-hemispheric in our TDC group which is consistent with previous developmental language literature (Friederici et al., 2011). A recent study using TMS measures of interhemispheric inhibition also supports such a later timing of lateralization in the motor system (Ciechanski and Kirton, 2017). This is also consistent with a "local" to "global" organizational change during development (Fair et al., 2009). This could account partially for the absence of significant age relationships with laterality in our sample since our laterality index measure was based on the comparison of long-range intra-hemispheric connectivity strengths between hemispheres, something that has been shown to develop later in adolescence and early adulthood (Friederici et al., 2011). Further elucidation of how such developmental effects interact with stroke-related changes in language connectivity will require more powerful samples.

Children with left hemisphere stroke appeared to have functional connectivity strengths in their right hemispheres that were comparable to TDC. Since stroke-induced damage occurred so early in life, it is plausible that these children retained pre-language bi-hemispheric potential and/or developed a right-lateralization to compensate for left hemisphere damage. This could be considered particularly exciting evidence in support of compensatory developmental plasticity after early injury (Staudt et al., 2002). By contrast, children with right hemisphere strokes had a similar pattern of FC in their intact left hemispheres when compared to TDC. We also found that children with either a right or left stroke do not show the same extent of stronger inter- over intra-hemispheric connectivity that TDC children do. While this is most likely due to the stroke damage itself, it does suggest that children with stroke may be experiencing a missing or delayed portion of language network development that TDC children have.

In addition to cortical differences in connectivity, we also observed that IFG connectivity with subcortical areas such as the anterior thalamus and caudate nucleus may be weaker in stroke participants as compared to TDC. Specifically, differences appeared to be localized to the left ventral anterior nucleus of the thalamus though this requires confirmation with a larger sample. These findings are consistent with the thalamus, striatum and basal ganglia playing an important role in thalamo-cortical circuits mediating language function (Klostermann et al., 2013). This may be further functional evidence of a disruption of the direct motor pathway after stroke in children manifesting as language dysfunction without frank dysphasia, possibly related to the injury occurring before language networks have been established.

This raises interesting questions such as whether there are any functional deficits in children with right-sided stroke that fall within the domains traditionally thought of as being mediated by the right hemisphere. Further, if language function resides in the right hemisphere after left hemisphere stroke, according to the "functional crowding hypothesis", non-verbal functions such as visual-spatial skills or non-verbal memory may show deficits that have been hypothesized to result from secondary "overcrowding" in the compensating right hemisphere (Lansdell, 1969). Our results suggest that this is not the case since visual memory appeared to be within the average range (29-40th percentiles compared to TDC peers). However, we did not exhaustively test such functions and more in-depth evaluations of other specifically right hemisphere tasks including visual-spatial skills or prosody and intonation processing (Brauer and Friederici, 2007; Friederici and Alter, 2004) may shed more light on this question.

Surprisingly, we did not observe significant relationships between measures of expressive language function and FC strength. Specifically, measures such as vocabulary and word generation did not appear to be related to FC. This may be due to low performance on some of these measures (8th-22nd percentiles) which did not provide enough variability to tease out a correlation. We found instead that tasks with a substantial comprehension component appeared to be more related to both inter- and intra-hemispheric FC. A related question is how specific our NP testing was in terms of evaluating language function. Specifically, what are the complementary roles that attention and memory play during NP testing in this population? Could it be that the observed "language" deficits also embody deficits in processing speed, working memory and syntactic processing (Makuuchi and Friederici, 2013). We found that processing speed was very low (13th percentile) in our sample, however verbal memory performance appeared to be average (59th-61st percentiles). Given that processing speed was impaired in these children after stroke it may be that the timed word generation tasks were particularly difficult and that untimed tasks give a better measure of function, relatively independent of processing speed deficits. Perhaps a more complex language testing battery could comment more specifically on higher-level language functions (Ballantyne et al., 2008, 2007; Lee et al., 2005; Reilly et al., 1998, Reilly et al., 2013; Westmacott et al., 2010).

We have also demonstrated that children with PVI and injury isolated to the subcortical white matter often demonstrate language network FC more comparable to TDC. The more extensive cortical and subcortical damage caused by infarction of the middle cerebral artery in children with AIS is the major difference between these two groups. Interestingly, lesion size in AIS was not correlated with language performance suggesting that it is not necessarily the size of the stroke lesion that causes language deficits, but rather the location. Timing of

injury is another fundamental difference between the lesion types where the earlier occurrence of PVI lesions has been shown to relatively spare other functional pathways such as somatosensation (Kuczynski et al., 2017; Kuczynski et al., 2018; Staudt, 2007). That the major language pathways are often spared by all but the largest PVI lesions is another consideration. These results are consistent with the generally favourable outcomes described in the limited studies of PVI to date (Kirton et al., 2008).

Our study has potential implications for both therapeutic language interventions and instructional strategies after perinatal stroke (Schlaug, 2018). It appears that reduced functional connectivity may subsequently lead to deficits in comprehension tasks. Accordingly, specific testing followed by instructional techniques tailored to strengthen these abilities might improve outcomes for affected children. Taking "timed" components out of tasks may help with deficits in processing speed. Further, language studies involving children who incur a stroke later in childhood during the more critical language development phases might combine investigations of clinical outcomes and functional imaging to better understand interventions in related pediatric populations (such as intensive speech therapy and non-invasive brain stimulation) (Barwood et al., 2011; Carlson et al., 2016; Hamilton et al., 2011; Mylius et al., 2012; Naeser et al., 2012; Torres et al., 2013; Zumbansen and Thiel, 2014) to maximize compensatory plasticity.

Our seeds for FC analyses were selected based on anatomical structures using an established atlas rather than through task-based functional MRI. Ideally, identification of language areas would have been determined through a functional localizer task. However, given the high degree of connectivity between ROIs in the non-lesioned hemisphere, it is likely that these ROIs represent areas that are functionally connected, consistent with previous reports of re-organization after injury at birth (Staudt et al., 2002). Further, functional connectivity of language areas to the frontal pole reference seed was very low additionally suggesting functional specificity of the language areas. We also found an interesting dissociation between FC and performance on two memory scales. Specifically, performance on a verbal memory task (CMS Stories) was significantly related to functional connectivity between language areas, but performance on a visual memory task (CMS Faces) was not, again suggesting functional specificity of the selected language areas.

Our study does have limitations that should be acknowledged. Our sample was quite possibly biased toward older and more highly-functioning participants due to the requirement that they had to remain still during the MRI scan. Further, a higher number of male participants and those that had left hemisphere stroke were included. This disparity is reflective of naturally occurring incidence rates, however afforded more statistical power for the left hemisphere stroke group over the right. The subset of children with stroke that completed clinical NP cognitive testing were typically more severely affected patients (necessitating a clinical referral for neuropsychological testing) but not so severe that they could not complete the cognitive tasks required. This likely led to a systematic difference between the sample that completed cognitive testing and those that did not. The resulting sample was admittedly small due to the observational nature of the study and correlations between cognitive function and functional connectivity should be considered with this small sample size in mind (even given the non-parametric statistics employed). We also combined the AIS and PVI groups in this analysis to maximize statistical power. Since we were interested in investigating compensatory neuroplasticity after injury, we felt that it was acceptable to combine stroke types when investigating cognitive functioning. This probably introduced additional variability given that both the mechanism (arterial vs venous infarction) and lesion sizes were different between the two groups even though time of injury was very similar (perinatal). This additional variability also allowed us to tease out relationships between cognitive function and FC something that may not have been possible with a smaller and more homogeneous sample. Moving forward, a prospective study would ideally require cognitive testing of all patients to gain a robust sample and allow statistically powerful comparisons between stroke types. In addition, most of the children with cognitive testing had left hemisphere strokes and so therefore may not be entirely representative of the larger perinatal stroke population. Lastly, measures we included to characterize level of functioning have a language component themselves (i.e., WISC-IV Full scale IQ estimates included the Vocabulary subtest).

For the functional connectivity analysis, a wider network of language areas could have been utilized. We used six atlas-based seeds but a more fine-grained collection of smaller seeds might have teased out additional information. We chose to use larger seeds (to maximize signal) from a well validated atlas to select our regions, however customized ROIs could have been drawn on a template and applied to each patient. Task fMRI localizers could also have been used to more closely tailor seed placement to each patient however this would have been less standardized across patients. Network metrics could also have been used to measure more global outcomes such as degree centrality at a group level (Xiao et al., 2015) or "small world" metrics and community detection algorithms (Fair et al., 2009) though this would require a much larger sample. Given the heterogeneity of the stroke lesions, this would have been challenging but may have given insight into compensatory changes in the larger language network.

In summary, we have shown in a sample of children with perinatal stroke that language network development is altered, often involving the contralesional hemisphere but potentially approximating typically developing children. This illustrates the remarkable neuroplastic capacity of the developing brain.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101861.

Conflicts of interest

Brian Brooks receives royalties for the sales of the Pediatric Forensic Neuropsychology textbook (2012, Oxford University Press) and three pediatric neuropsychological tests [Child and Adolescent Memory Profile (ChAMP, Sherman and Brooks, 2015, PAR Inc.), Memory Validity Profile (MVP, Sherman and Brooks, 2015, PAR Inc.), and Multidimensional Everyday Memory Ratings for Youth (MEMRY, Sherman and Brooks, 2017, PAR Inc.)]. He has previously received in-kind support (free test credits) from the publisher of the computerized cognitive test (CNS Vital Signs, Chapel Hill, North Carolina) used in this study. None of the authors have a financial interest in any measures used in the present study. None of the other authors have any conflicts of interest to declare.

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